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Patients do not typically develop Parkinson's Disease (PD) until they lose approximately 70% of their dopaminergic neurons. This neural degeneration typically manifests as motor symptoms. Yet, it is possible that subtle cognitive symptoms may precede onset of these motor symptoms. However, it remains unclear as to what early cognitive symptoms might be. Many of the neuropsychological changes reported with PD are not typically seen early in the disease and they are not seen in all subjects. Therefore, there is a need to develop new cognitive tests of PD that precede motor symptoms, are easy to administer and are valid early predictors. In order to develop cognitive tests that predict the onset of the motor deficits associated with Parkinson's Disease it is important to understand the effect of the dopaminergic system on the cortex. One possible action of dopamine on the cerebral cortex is that it increases signal to noise ratio. Changing this ratio may influence activation of semantic networks. Thus, we intend to study the semantic organization of verbal information in PD patients and matched controls. We will also induce dopamine blockade using Haldol in normal subjects, and assess these subjects for changes in the function of their semantic network.

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## Introduction

Patients do not typically develop Parkinson's Disease (PD) until they lose approximately 70% of their dopaminergic neurons. This neural degeneration typically manifests as the motor symptoms which are characteristic of PD. Yet, it is possible that subtle cognitive symptoms may precede the onset of the motor symptoms. In addition, screening for cognitive symptoms may be logistically easier than screening for motor deficits. However, it remains unclear as to what the early cognitive symptoms might be. There have been many excellent neuropsychological studies of patients with PD. These studies have revealed that patients with PD do have neuropsychological defects such as visuospatial disorders and evidence of frontal subcortical dysfunction. However, many of the neuropsychological changes reported with PD are not typically seen early in the disease and they are not seen in all subjects. Therefore, there is a need to develop new cognitive tests of PD that precede the motor symptoms, are easy to administer and are valid early predictors. In our research proposal we plan to develop cognitive tests that may be valid and reliable indicators of impending PD. In order to develop cognitive tests that predict the onset of the motor deficits associated with Parkinson's disease it is important to understand the effect of the dopaminergic system on the cortex. One possible action of dopamine on the cerebral cortex is that it increases the signal to noise ratio. Changing this ratio may influence activation of the semantic networks. If cortical levels of dopamine are influencing priming, one would expect that patients with PD would have stronger priming for indirect words than would controls. In addition, the direct relationship may also be weakened in patients with PD. In this study, we will attempt to learn if patients with PD, when compared to control subjects, prime differently. We also plan to learn if PD performance is different when they are on and off L-dopa. We will further assess relationships in the semantic net by having experimental and control subjects judge the relatedness of words. To test self activation of the semantic net, we will assess word generation in these subjects. We will also study PD patients and matched controls ability to inhibit the semantic net through their ability to complete sentences with unrelated words and generate unrelated words. Finally, we will induce dopamine blockade using Haldol in normal subjects, and test these subjects for changes in the function of their semantic network using the same tasks discussed above.

## Body

We have spent the first year of this grant in test development. This activity involved reviewing the current literature on verbal and semantic priming, and deriving appropriate tasks to address our hypotheses regarding semantic priming in PD. This review culminated in a selection of word pairs and word primes (Balota & Lorch, 1986, Bennett & McEvoy, in press, McNamara, 1992, McRae & Boisvert, 1998, Nelson et al., 1998, Shelton & Martin, 1992) for our relatedness judgment task and word generation tasks, which have some normative basis, and will allow us to assess differences in strength of verbal relatedness, and differences in strength of verbal mediation. These tests include a word priming task which requires the subject to identify a stimulus as either a real word or a nonsense word. Another test involves having the subject determine the degree of relatedness between to words that have been preselected based on normative-based judgments of relatedness. A third task involves having the subject generate a single word to a stimulus cue that has been preselected based on a normative-based assessment of semantic activation of that cue. This review has also provided us with a list of semantic categories that have normative data for our additional word generation tasks (Battig and Montegue, 1969). The tests derived from this list of categories require the subject to the generate exemplars that either match or do not match the target category. As part of this process, we have developed computer programs for the administration of some of these tasks that will facilitate data collection and analysis. We have also begun developing referral sources from which to recruit subjects for this study. We initiated data collection at the end of the first year of this grant.

We have spent the second year of this study with subject recruitment and data collection. Subject recruitment has involved daily patient screening in the Neurology Clinics of both Shands Hospital at the University of Florida, and the Malcolm Randal VAMC. We have recently initiated contacts with the Neurology Clinics at the Lake City VAMC and the University of Florida Health Science Center at Jacksonville to begin subject recruitment through these respective locations. The University of Florida Health Science Center Institutional Review Board (IRB) approval for these recruitment sites is currently in process, and actual subject recruitment will not commence at these later two locations until IRB approval is attained. Data collection has occurred with 17 volunteers, including seven men and three women with Parkinson's Disease, and three men and four women as control subjects. However, we have had some difficulty recruiting appropriate control subjects, and having Parkinsonian patients return "off" their PD medications, thus resulting in incomplete data. Consequently, we do not have any reportable data at this time. Nevertheless, in the coming year, we intend to continue recruiting subjects and collecting data in the broader North Central Florida area to achieve the stated research goals.

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